PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C07D 333/36, 231/40, 235/30, A61K 31/38, 31/415 — A1

(11) International Publication Number: **WO 99/23091**

(43) International Publication Date: 14 May 1999 (14.05.99)

(21) International Application Number: PCT/US98/22907

(22) International Filing Date: 29 October 1998 (29.10.98)

(30) Priority Data:
60/064,102 3 November 1997 (03.11.97) US

(71) Applicant: BOEHRINGER INGELHEIM PHARMACEUTICALS, INC. [US/US]; 900 Ridgebury Road, Ridgefield, CT 06877 (US).

(72) Inventors: REGAN, John, R.; 287 Rockingstone Avenue, Larchmont, NY 10538 (US). CIRILLO, Pier, F.; 180 Washington Road, Woodbury, CT 06798 (US). HICKEY, Eugene, R.; 5 Woodbury Drive, Danbury, CT 06811 (US). MOSS, Neil; 199 Barlow Moutain Road, Ridgefield, CT 06877 (US). CYWIN, Charles, L.; 37 Quaker Ridge Road, Bethel, CT 06801 (US). PARGELLIS, Christopher; 18 Limekiln Road, Redding, CT 06896 (US). GILMORE, Thomas, A.; 160 Christian Road, Middlebury, CT 06762 (US).

(74) Agents: RAYMOND, Robert et al.; Boehringer Ingelheim Pharmaceuticals, Inc., 900 Ridgebury Road, P.O. Box 368, Ridgefield, CT 06877 (US).

(81) Designated States: AU, BG, BR, BY, CA, CN, CZ, HR, HU, ID, IL, JP, KR, KZ, LT, LV, MX, NO, NZ, PL, RO, RU, TR, UA, UZ, VN, YU, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: AROMATIC HETEROCYCLIC COMPOUNDS AS ANTI–INFLAMMATORY AGENTS

(57) Abstract

Novel aromatic heterocyclic compounds inhibit cytokines production involved in immunoregulation and inflammation such as interleukin–1 and tumor necrosis factor production. The compounds are therefore useful in pharmaceutic compositions for treating diseases or pathological conditions involving inflammation such as chronic inflammatory diseases.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	**ES**	Spain	**LS**	Lesotho	**SI**	Slovenia
AM	Armenia	**FI**	Finland	**LT**	Lithuania	**SK**	Slovakia
AT	Austria	**FR**	France	**LU**	Luxembourg	**SN**	Senegal
AU	Australia	**GA**	Gabon	**LV**	Latvia	**SZ**	Swaziland
AZ	Azerbaijan	**GB**	United Kingdom	**MC**	Monaco	**TD**	Chad
BA	Bosnia and Herzegovina	**GE**	Georgia	**MD**	Republic of Moldova	**TG**	Togo
BB	Barbados	**GH**	Ghana	**MG**	Madagascar	**TJ**	Tajikistan
BE	Belgium	**GN**	Guinea	**MK**	The former Yugoslav Republic of Macedonia	**TM**	Turkmenistan
BF	Burkina Faso	**GR**	Greece			**TR**	Turkey
BG	Bulgaria	**HU**	Hungary	**ML**	Mali	**TT**	Trinidad and Tobago
BJ	Benin	**IE**	Ireland	**MN**	Mongolia	**UA**	Ukraine
BR	Brazil	**IL**	Israel	**MR**	Mauritania	**UG**	Uganda
BY	Belarus	**IS**	Iceland	**MW**	Malawi	**US**	United States of America
CA	Canada	**IT**	Italy	**MX**	Mexico	**UZ**	Uzbekistan
CF	Central African Republic	**JP**	Japan	**NE**	Niger	**VN**	Viet Nam
CG	Congo	**KE**	Kenya	**NL**	Netherlands	**YU**	Yugoslavia
CH	Switzerland	**KG**	Kyrgyzstan	**NO**	Norway	**ZW**	Zimbabwe
CI	Côte d'Ivoire	**KP**	Democratic People's Republic of Korea	**NZ**	New Zealand		
CM	Cameroon			**PL**	Poland		
CN	China	**KR**	Republic of Korea	**PT**	Portugal		
CU	Cuba	**KZ**	Kazakstan	**RO**	Romania		
CZ	Czech Republic	**LC**	Saint Lucia	**RU**	Russian Federation		
DE	Germany	**LI**	Liechtenstein	**SD**	Sudan		
DK	Denmark	**LK**	Sri Lanka	**SE**	Sweden		
EE	Estonia	**LR**	Liberia	**SG**	Singapore		

AROMATIC HETEROCYCLIC COMPOUNDS AS ANTI-INFLAMMATORY AGENTS

TECHNICAL FIELD OF THE INVENTION

The invention relates to aromatic heterocyclic compounds which inhibit the release of inflammatory cytokines such as interleukin-1 and tumor necrosis factor from cells and are thus useful for treating diseases and pathological conditions involving inflammation such as chronic inflammatory disease. The invention also relates to processes for preparing such compounds and pharmaceutical compositions comprising them.

BACKGROUND OF THE INVENTION

Tumor necrosis factor (TNF) and interleukin-1 (IL-1) are important biological entities collectively referred to as proinflammatory cytokines. These, along with several other related molecules, mediate the inflammatory response associated with the immunological recognition of infectious agents. The inflammatory response plays an important role in limiting and controlling pathogenic infections.

Elevated levels of proinflammatory cytokines are associated with a number of diseases of autoimmunity such as toxic shock syndrome, rheumatoid arthritis, osteoarthritis, diabetes and inflammatory bowel disease (Dinarello, C.A., *et al.*, 1984, *Rev. Infect. Disease 6*:51). In these diseases, chronic elevation of inflammation exacerbates or causes much of the pathophysiology observed. For example, rheumatoid synovial tissue becomes invaded with inflammatory cells that result in destruction to cartilage and bone (Koch, A.E., *et al.*, 1995, *J. Invest. Med. 43*: 28-38). An important and accepted therapeutic approach for potential drug intervention in these diseases is the reduction of proinflammatory cytokines such as TNF (also referred to in its secreted, cell-free form termed TNFα) and IL-1β. A number of anti-cytokine therapies are currently in clinical trials. Efficacy has been demonstrated with a monoclonal antibody directed against TNF in a number of autoimmune diseases (Heath, P., "CDP571: An Engineered Human IgG4 Anti-TNFα Antibody" IBC Meeting on Cytokine Antagonists, Philadelphia, PA, April 24-5, 1997). These include the treatment of rheumatoid arthritis, Crohn's disease

and ulcerative colitis (Rankin, E.C.C., *et al.*, 1997, *British J. Rheum. 35*: 334-342 and Stack, W.A., *et al.*, 1997, *Lancet 349*: 521-524). The monoclonal antibody is thought to function by binding to both soluble TNFα and to membrane bound TNF.

A soluble TNFα receptor has been engineered that interacts with TNFα. The approach is similar to that described above for the monoclonal antibodies directed against TNFα; both agents bind to soluble TNFα, thus reducing its concentration. One version of this construct, called Enbrel (Immunex, Seattle, WA) recently demonstrated efficacy in a Phase III clinical trial for the treatment of rheumatoid arthritis (Brower *et al.*, 1997, *Nature Biotechnology 15*: 1240). Another version of the TNFα receptor, Ro 45-2081 (Hoffman-LaRoche Inc., Nutley, NJ) has demonstrated efficacy in various animal models of allergic lung inflammation and acute lung injury. Ro 45-2081 is a recombinant chimeric molecule constructed from the soluble 55 kDa human TNF receptor fused to the hinge region of the heavy chain IgG1 gene and expressed in eukaryotic cells (Renzetti, *et al.*, 1997, *Inflamm. Res. 46*: S143).

IL-1 has been implicated as an immunological effector molecule in a large number of disease processes. IL-1 receptor antagonist (IL-1ra) had been examined in human clinical trials. Efficacy has been demonstrated for the treatment of rheumatoid arthritis (Antril, Amgen). In a phase III human clinical trial IL-1ra reduced the mortality rate in patients with septic shock syndrome (Dinarello, 1995, *Nutrution 11*, 492). Osteoarthritis is a slow progressive disease characterized by destruction of the articular cartilage. IL-1 is detected in synovial fluid and in the cartilage matrix of osteoarthritic joints. Antagonists of IL-1 have been shown to diminish the degradation of cartilage matrix components in a variety of experimental models of arthritis (Chevalier, 1997, *Biomed Pharmacother. 51*, 58). Nitric oxide (NO) is a mediator of cardiovascular homeostasis, neurotransmission and immune function; recently it has been shown to have important effects in the modulation of bone remodeling. Cytokines such as IL-1 and TNF are potent stimulators of NO production. NO is an important regulatory molecule in bone with effects on cells of the osteoblast and osteoclast lineage (Evans, *et al.*, 1996, *J Bone Miner Res. 11*, 300). The promotion of beta-cell destruction leading to insulin dependent diabetes mellitis shows dependence on IL-1. Some of this damage

may be mediated through other effectors such as prostaglandins and thromboxanes. Il-1 can effect this process by controlling the level of both cyclooxygenase II and inducible nitric oxide synthetase expression (McDaniel *et al.,* 1996, *Proc Soc Exp Biol Med. 211*, 24). Elevation of several cytokines have been demonstrated during active inflammatory bowel disease (IBD). A mucosal imbalance of intestinal IL-1 and IL-1ra is present in patients with IBD. Insufficient production of endogenous IL-1ra may contribute to the pathogenesis of IBD (Cominelli, *et al.,* 1996, *Aliment Pharmacol Ther. 10*, 49). Alzheimer disease is characterized by the presence of beta-amyloid protein deposits, neurofibrillary tangles and cholinergic dysfunction throughout the hippocampal region. The structural and metabolic damage found in Alzheimer disease is due to a sustained elevation of IL-1 (Holden, *et al.,* 1995, *Med Hypootheses 45*, 559). A role for IL-1 in the pathogenesis of human immunodeficiency virus (HIV) has been identified. IL-1ra showed a clear relationship to acute inflammatory events as well as to the different disease stages in the pathophysiology of HIV infection (Kreuzer, *et al.,* 1997, *Clin Exp Immunol. 109*, 54). IL-1 and TNF are both involved in periodontal disease. The distructive process associated with peridontal disease may be due to a disregulation of both IL-1 and TNF (Howells, 1995, *Oral Dis. 1*, 266).

Proinflammatory cytokines such as TNFα and IL-1β are also important mediators of septic shock and associated cardiopulmonary dysfunction, acute respiratory distress syndrome (ARDS) and multiple organ failure. TNFα has also been implicated in cachexia and muscle degradation, associated with HIV infection (Lahdiverta *et al.*, 1988, *Amer. J. Med., 85*, 289). Obesity is associated with an increase incidence of infection, diabetes and cardiovascular disease. Abnormalities in TNFα expression have been noted for each of the above conditions (Loffreda, *et al.,* 1998, *FASEB J. 12*, 57). It has been proposed that elevated levels of TNFα are involved in other eating related disorders such as anorexia and bulimia nervosa. Pathophysiological parallels are drawn between anorexia nervosa and cancer cachexia (Holden, *et al.,* 1996, *Med Hypotheses 47*, 423). An inhibitor of TNFα production, HU-211, was shown to improve the outcome of closed brain injury in an experimental model (Shohami, *et al.,* 1997, *J Neuroimmunol. 72*, 169). Atherosclerosis is known to have an inflammatory component and cytokines such as IL-1 and TNF have been suggested to promote the

disease. In an animal model an IL-1 receptor antagonist was shown to inhibit fatty streak formation (Elhage *et al.*, 1998, *Circulation, 97*, 242).

The abnormal expression of inducible nitric oxide synthetase (iNOS) has been associated with hypertension in the spontaneously hypertensive rat (Chou *et al.*, 1998, *Hypertension, 31*, 643). IL-1 has a role in the expression of iNOS and therefore may also have a role in the pathogenesis of hypertension (Singh *et al.*, 1996, *Amer. J. Hypertension, 9*, 867).

IL-1 has also been shown to induce uveitis in rats which could be inhibited with IL-1 blockers. (Xuan et al., 1998, *J. Ocular Pharmacol. and Ther.*, *14*, 31). Cytokines including IL-1, TNF and GM-CSF have been shown to stimulate proliferation of acute myelogenous leukemia blasts (Bruserud, 1996, *Leukemia Res. 20*, 65). IL-1 was shown to be essential for the development of both irritant and allergic contact dermatitis. Epicutaneous sensitization can be prevented by the administration of an anti- IL-1 monoclonal antibody before epicutaneous application of an allergen (Muller, *et al.*, 1996, *Am J Contact Dermat. 7*, 177). Data obtained from IL-1 knock out mice indicates the critical involvement in fever for this cytokine (Kluger *et al.*, 1998, *Clin Exp Pharmacol Physiol. 25*, 141). A variety of cytokines including TNF, IL-1, IL-6 and IL-8 initiate the acute-phase reaction which is stereotyped in fever, malaise, myalgia, headaches, cellular hypermetabolism and multiple endocrine and enzyme responses (Beisel, 1995, *Am J Clin Nutr. 62*, 813). The production of these inflammatory cytokines rapidly follows trauma or pathogenic organism invasion.

Other proinflammatory cytokines have been correlated with a variety of disease states. IL-8 correlates with influx of neutrophils into sites of inflammation or injury. In consequence, IL-8 has a role in acute respiratory response syndrome (ARDS) and in cerebral reperfusion injury (Matsumoto, *et al.*, 1997, *Journal of Leukocyte Biology 62:* 581). Blocking antibodies against IL-8 have demonstrated a role for IL-8 in the neutrophil associated tissue injury in acute inflammation (Harada *et al.*, 1996: *Molecular Medicine Today 2*: 482). Rhinovirus triggers the production of various

proinflammatory cytokines, predominantly IL-8, which results in symptomatic illnesses such as acute rhinitis (Winther *et al.*, 1998, *Am J Rhinol. 12*, 17).

Other diseases that are effected by IL-8 include myocardial ischemia and reperfusion, inflammatory bowel disease and many others.

The proinflammatory cytokine IL-6 has been implicated with the acute phase response. IL-6 is a growth factor in a number in oncological diseases including multiple myeloma and related plasma cell dyscrasias (Treon, *et al.*, 1998, *Current Opinion in Hematology 5*: 42). It has also been shown to be an important mediator of inflammation within the central nervous system. Elevated levels of IL-6 are found in several neurological disorders including AIDS dememtia complex, Alzheimer's disease, multiple sclerosis, systemic lupus erythematosus, CNS trauma and viral and bacterial meningitis (Gruol, *et al.*, 1997, *Molecular Neurobiology 15*: 307). IL-6 also plays a significant role in osteoporosis. In murine models it has been shown to effect bone resorption and to induce osteoclast activity (Ershler *et al.*, 1997, *Development and Comparative Immunol. 21*: 487). Marked cytokine differences, such as IL-6 levels, exist in vivo between osteoclasts of normal bone and bone from patients with Paget's disease (Mills, *et al.*, 1997, *Calcif Tissue Int. 61*, 16). A number of cytokines have been shown to be involved in cancer cachexia. The severity of key parameters of cachexia can be reduced by treatment with anti IL-6 antibodies or with IL-6 receptor antagonists (Strassmann, *et al.*, 1995, *Cytokins Mol Ther. 1*, 107). Several infectious diseases, such as influenza, indicate IL-6 and IFN alpha as key factors in both symptom formation and in host defense (Hayden, *et al.*, 1998, *J Clin Invest. 101*, 643). Overexpression of IL-6 has been implicated in the pathology of a number of diseases including multiple myeloma, rheumatoid arthritis, Castleman's disease, psoriasis and post-menopausal osteoporosis (Simpson, *et al.*, 1997, *Protein Sci. 6*, 929). Compounds that interfered with the production of cytokines including IL-6, and TNF were effective in blocking a passive cutaneous anaphylaxis in mice (Scholz *et al.*, 1998, *J. Med. Chem., 41*, 1050).

GM-CSF is another proinflammatory cytokine with relevance to a number of therapeutic diseases. It influences not only proliferation and differentiation of stem

cells but also regulates several other cells involved in acute and chronic inflammation. Treatment with GM-CSF has been attempted in a number of disease states including burn-wound healing, skin-graft resolutiona as well as cytostatic and radiotherapy induced mucositis (Masucci, 1996, *Medical Oncology 13*: 149). GM-CSF also appears to play a role in the replication of human immunodeficiency virus (HIV) in cells of macrophage lineage with relevance to AIDS therapy (Crowe *et al.*, 1997, *Journal of Leukocyte Biology 62*: 41). Bronchial asthma is characterised by an inflammatory process in lungs. Involved cytokines include GM-CSF amongst others (Lee, 1998, *J R Coll Physicians Lond 32*, 56).

Interferon γ (IFN γ) has been implicated in a number of diseases. It has been associated with increased collagen deposition that is a central histopathological feature of graft-versus-host disease (Parkman, 1998, *Curr Opin Hematol. 5*, 22). Following kidney transplantation, a patient was diagnosed with acute myelogenous leukemia. Retrospective analysis of peripheral blood cytokines revealed elevated levels of GM-CSF and IFN γ. These elevated levels coincided with a rise in peripheral blood white cell count (Burke, *et al.*, 1995, *Leuk Lymphoma. 19*, 173). The development of insulin-dependent diabetes (Type 1) can be correlated with the accumulation in pancreatic islet cells of T-cells producing IFN γ (Ablumunits, *et al.*, 1998, *J Autoimmun. 11*, 73). IFN γ along with TNF, IL-2 and IL-6 lead to the activation of most peripheral T-cells prior to the development of lesions in the central nervous system for diseases such as multiple sclerosis (MS) and AIDS dementia complex (Martino *et al.*, 1998, *Ann Neurol. 43*, 340). Atherosclerotic lesions result in arterial disease that can lead to cardiac and cerebral infarction. Many activated immune cells are present in these lesions, mainly T-cells and macrophages. These cells produce large amounts of proinflammatory cytokines such as TNF, IL-1 and IFN γ. These cytokines are thought to be involved in promoting apoptosis or programmed cell death of the surrounding vascular smooth muscle cells resulting in the atherosclerotic lesions (Geng, 1997, *Heart Vessels Suppl 12*, 76). A reduced production of IFN γ is associated with onset of allergic disease in infants (Warner *et al.*, 1997, *Pediatr Allergy Immunol. 8*, 5). Allergic subjects produce mRNA specific for IFN γ following challenge with Vespula venom (Bonay, *et al.*, 1997, *Clin Exp Immunol. 109*, 342). The expression of a number of cytokines, including IFN

γ has been shown to increase following a delayed type hypersensitivity reaction thus indicating a role for IFN γ in atopic dermatitis (Szepietowski, *et al.*, 1997, *Br J Dermatol. 137*, 195). Histopathologic and immunohistologic studies were performed in cases of fatal cerebral malaria. Evidence for elevated IFN γ amongst other cytokines was observed indicating a role in this disease (Udomsangpetch *et al.*, 1997, *Am J Trop Med Hyg. 57*, 501). The importance of free radical species in the pathogenesis of various infectious diseases has been established. The nitric oxide synthesis pathway is activated in response to infection with certain viruses via the induction of proinflammatory cytokines such as IFN γ (Akaike, *et al.*, 1998, *Proc Soc Exp Biol Med. 217*, 64). Patients, chronically infected with hepatitis B virus (HBV) can develop cirrhosis and hepatocellular carcinoma. Viral gene expression and replication in HBV transgenic mice can be suppressed by a post-transcriptional mechanism mediated by IFN γ, TNF and IL-2 (Chisari, *et al.*, 1995, *Springer Semin Immunopathol. 17*, 261). IFN γ can selectively inhibit cytokine induced bone resorption. It appears to do this via the intermediacy of nitric oxide (NO) which is an important regulatory molecule in bone remodeling. NO may be involved as a mediator of bone disease for such diseases as: the rheumatoid arthritis, tumor associated osteolysis and postmenopausal osteoporosis (Evans, *et al.*, 1996, *J Bone Miner Res. 11*, 300). Studies with gene deficient mice have demonstrated that the IL-12 dependent production of IFN γ is critical in the control of early parasitic growth. Although this process is independent of nitric oxide the control of chronic infection does appear to be NO dependent (Alexander *et al.*, 1997, *Philos Trans R Soc Lond B Biol Sci 352*, 1355). NO is an important vasodilator and convincing evidence exists for its role in cardiovascular shock (Kilbourn, *et al.*, 1997, *Dis Mon. 43*, 277). IFN γ is required for progression of chronic intestinal inflammation in such diseases as Crohn's disease and inflammatory bowel disease (IBD) presumably through the intermediacy of CD4+ lymphocytes probably of the TH1 phenotype (Sartor 1996, *Aliment Pharmacol Ther. 10 Suppl 2*, 43). Treatment of patients with IFN has demonstrated efficacy in a number of diseases including Behcet's disease which is a multisystem vasculitis. Interestingly in a small patient study for uveitis treatment with IFN γ was essentially ineffective (Kotter, *et al.*, 1996, *Ger J Ophthalmol. 5*, 92). A number of cancers can be treated with IFN γ, this includes the treatment of multiple myeloma. Much of the effect is apparently dependent on IL-6 which is a central

myeloma growth factor (Palumbo *et al.*, 1995, *Leuk Lymphoma 18*, 215). An elevated level of serum IgE is associated with various atopic diseases such as bronchial asthma and atopic dermatitis. The level of IFN γ was negatively correlated with serum IgE suggesting a role for IFN γ in atopic patients (Teramoto *et al.*, 1998, *Clin Exp Allergy 28*, 74).

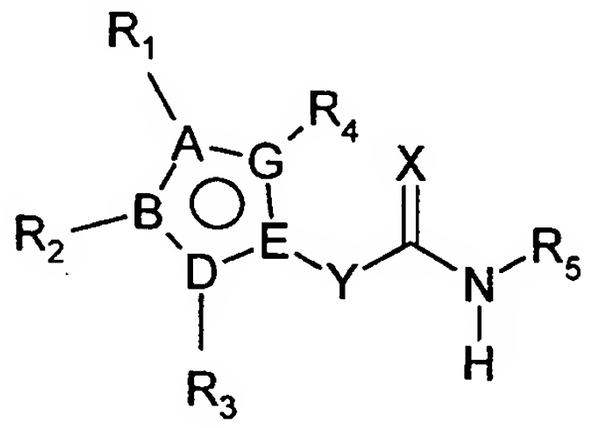
The work cited above supports the principle that inhibition of cytokine production will be beneficial in the treatment of various disease states. Some protein therapeutics are in late development or have been approved for use in particular diseases. Protein therapeutics are costly to produce and have bioavailability and stability problems. Therefore a need exists for new small molecule inhibitors of cytokine production with optimized efficacy, pharmacokinetic and safety profiles.

BRIEF DESCRIPTION OF THE INVENTION

The inventon provides novel compounds which inhibit the release of inflammatory cytokines such as interleukin-1 and tumor necrosis factor from cells and which are thus useful for treating diseases and pathological conditions involving inflammation such as chronic inflammatory disease.

DETAILED DESCRIPTION OF THE INVENTION

In its broadest generic aspect, the invention provides novel compounds of the formula I



(I)

wherein:

A is C or N;

B is C, N, O or S;

D is C, N or S;

E is C or N;

G is C, S or N;

X is S, O or NR_6;

Y is CHR_7 or N-H;

R_1 is selected from the group consisting of:

(a) C_{3-10} branched alkyl, which is optionally partially or fully halogenated, and optionally substituted with one to three phenyl, naphthyl or heteroaryl groups (each such heteroaryl group being independently selected from pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrrolyl, imidazolyl, pyrazolyl, thienyl, furyl, isoxazolyl and isothiazolyl), each such phenyl, naphthyl or heteroaryl group being substituted with 0 to 5 groups selected from halogen, C_{1-6} branched or unbranched alkyl which

is optionally partially or fully halogenated, C_{3-8} cycloalkyl, C_{5-8} cycloalkenyl, hydroxy, cyano, C_{1-3} alkyloxy which is optionally partially or fully halogenated, aminocarbonyl and di(C_{1-3})alkylaminocarbonyl;

(b) a cycloalkyl group selected from cyclopropyl, cyclobutyl, cyclopentanyl, cyclohexanyl, cycloheptanyl, bicyclopentanyl, bicyclohexanyl and bicycloheptanyl, which cycloalkyl group is optionally partially or fully halogenated and which is optionally substituted with one to three C_{1-3} alkyl groups, or an analog of such cycloalkyl group wherein instead of one to three ring methylene groups there are groups independently selected from O, S, CHOH, >C=O, >C=S and NH;

(c) C_{3-10} branched alkenyl which is optionally partially or fully halogenated, and which is optionally substituted with one to three groups independently selected from C_{1-5} branched or unbranched alkyl, phenyl, naphthyl or heteroaryl, with each such heteroaryl group being independently selected from pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrrolyl, imidazolyl, pyrazolyl, thienyl, furyl, isoxazolyl and isothiazolyl, and each such phenyl, naphthyl or heteroaryl group being substituted with 0 to 5 groups selected from halogen, C_{1-6} branched or unbranched alkyl which is optionally partially or fully halogenated, cyclopropyl, cyclobutyl, cyclopentanyl, cyclohexanyl, cycloheptanyl, bicyclopentanyl, bicyclohexanyl, bicycloheptanyl, hydroxy, cyano, C_{1-3} alkyloxy which is optionally partially or fully halogenated, aminocarbonyl and mono- or di(C_{1-3})alkylaminocarbonyl;

(d) a cycloalkenyl group selected from cyclopentenyl, cyclohexenyl, cyclohexadienyl, cycloheptenyl, cycloheptadienyl, bicyclohexenyl and bicycloheptenyl, wherein such cycloalkenyl group is optionally substituted with one to three C_{1-3} alkyl groups;

(e) cyano; and,

(f) an alkoxy carbonyl group selected from methoxycarbonyl, ethoxycarbonyl and propoxycarbonyl;

R_2 is selected from the group consisting of the following, when B is a carbon atom or an amino nitrogen: hydrogen, C_{1-6} branched or unbranched alkyl which is optionally partially or fully halogenated, acetyl, benzoyl and phenylsulfonyl;

R_3 is selected from the group consisting of the following, when D is a carbon atom or an amino nitrogen:

a) phenyl, naphthyl and heteroaryl (wherein said heteroaryl group is selected from pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrrolyl, imidazolyl, pyrazolyl, thienyl, furyl, isoxazolyl, isothiazolyl, quinolinyl, isoquinolinyl, indolyl, benzimidazolyl, benzofuranyl, benzoxazolyl, benzisoxazolyl, benzpyrazolyl, benzothiofuranyl, cinnolinyl, pterindinyl, phthalazinyl, naphthypyridinyl, quinoxalinyl, quinazolinyl, purinyl and indazolyl), wherein such phenyl, naphthyl or heteroaryl group is optionally substituted with one to five groups independently selected from C_{1-6} branched or unbranched alkyl, phenyl, naphthyl, heteroaryl selected from the group set forth immediately above, C_{1-6} branched or unbranched alkyl which is optionally partially or fully halogenated, cyclopropyl, cyclobutyl, cyclopentanyl, cyclohexanyl, cycloheptanyl, bicyclopentanyl, bicyclohexanyl, bicycloheptanyl, phenyl C_{1-5} alkyl, naphthyl C_{1-5} alkyl, halo, hydroxy, cyano, C_{1-3} alkyloxy which is optionally partially or fully halogenated, phenyloxy, naphthyloxy, heteraryloxy wherein the heteroaryl moiety is selected from the group set forth above in this subparagraph, nitro, amino, mono- or di-(C_{1-3})alkylamino, phenylamino, naphthylamino, heteroarylamino wherein the heteroaryl moiety is selected from the group set forth above in this subparagraph, aminocarbonyl, a mono- or di-(C_{1-3})alkyl aminocarbonyl, C_{1-4} branched or unbranched alkyl oxycarbonyl, C_{1-5} alkylcarbonyl C_{1-4} branched or unbranched alkyl, amino C_{1-5} alkyl, mono- or di-(C_{1-3})alkylamino(C_{1-5})alkyl, aminosulfonyl, di-(C_{1-3})alkylaminosulfonyl;

b) fused aryl (selected from benzocyclobutanyl, indanyl, indenyl, dihydronaphthyl, tetrahydronaphthyl, benzocycloheptanyl and benzocycloheptenyl), and fused heteroaryl (selected from

cyclopentenopyridine, cyclohexanopyridine, cyclopentanopyrimidine, cyclohexanopyrimidine, cyclopentanopyrazine, cyclohexanopyrazine, cyclopentanopyridazine, cyclohexanopyridazine, cyclopentanoquinoline, cyclohexanoquinoline, cyclopentanoisoquinoline, cyclohexanoisoquinoline, cyclopentanoindole, cyclohexanoindole, cyclopentanobenzimidazole, cyclohexanobenzimidazole, cyclopentanobenzoxazole, cyclohexanobenzoxazole, cyclopentanoimidazole, cyclohexanoimidazole, cyclopentanothiophene and cyclohexanothiophene), wherein the fused aryl or fused heteroaryl ring is substituted with 0 to 3 groups independently selected from phenyl, naphthyl and heteroaryl (wherein each such heteroaryl is selected from pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrrolyl, imidazolyl, pyrazolyl, thienyl, furyl, isoxazolyl and isothiazolyl), C_{1-6} branched or unbranched alkyl which is optionally partially or fully halogenated, halo, cyano, C_{1-3} alkyloxy which is optionally partially or fully halogenated, phenyloxy, naphthyloxy, heteroaryloxy (wherein the heteroaryl moiety is selected from the group set forth above in this subparagraph), nitro, amino, mono- or di-(C_{1-3})alkylamino, phenylamino, naphthylamino, heteroarylamino (wherein the heteroaryl moiety is selected from the group set forth above in this subparagraph), aminocarbonyl, a mono- or di-(C_{1-3})alkyl aminocarbonyl, C_{1-4} branched or unbranched alkyl oxycarbonyl, C_{1-5} alkylcarbonyl C_{1-4} branched or unbranched alkyl, amino C_{1-5} alkyl, mono- or di-(C_{1-3})alkylamino(C_{1-5})alkyl, aminosulfonyl, di-(C_{1-3})alkylaminosulfonyl;

c) a cycloalkyl group selected from cyclopentanyl, cyclohexanyl, cycloheptanyl, bicyclopentanyl, bicyclohexanyl and bicycloheptanyl, which cycloalkyl group is optionally partially or fully halogenated and which is optionally substituted with one to three C_{1-3} alkyl groups;

d) a cycloalkenyl group selected from cyclopentenyl, cyclohexenyl, cyclohexadienyl, cycloheptenyl, cycloheptadienyl, bicyclohexenyl and bicycloheptenyl, wherein such cycloalkenyl group is optionally substituted with one to three C_{1-3} alkyl groups; and,

e) acetyl, benzoyl and phenylsulfonyl;

or R_1 and R_2 taken together may optionally form a fused phenyl or pyridinyl ring,

or R_2 and R_3 taken together may optionally form a fused phenyl or pyridinyl ring,

R_4 is selected from the following, when G is a carbon atom or an amino nitrogen: hydrogen and C_{1-6} branched or unbranched alkyl which is optionally partially or fully halogenated;

R_5 is selected from the group consisting of:

a) phenyl, naphthyl and heteroaryl (wherein such heteroaryl is selected from pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrrolyl, imidazolyl, pyrazolyl, thienyl, furyl, isoxazolyl, isothiazolyl, quinolinyl, isoquinolinyl, indolyl, benzimidazolyl, benzofuranyl, benzoxazolyl, benzisoxazolyl, benzpyrazolyl, benzothiofuranyl, cinnolinyl, pterindinyl, phthalazinyl, naphthypyridinyl, quinoxalinyl, quinazolinyl, purinyl and indazolyl), wherein such phenyl, naphthyl or heteroaryl group optionally bears one to five groups selected from phenyl, naphthyl and heteroaryl (wherein each such heteroaryl moiety is independently selected from the group defined above in this subparagraph), C_{1-6} branched or unbranched alkyl which is optionally partially or fully halogenated, cyclopropyl, cyclobutyl, cyclopentanyl, cyclohexanyl, cycloheptanyl, bicyclopentanyl, bicyclohexanyl, bicycloheptanyl, halo, cyano, C_{1-3} alkyloxy which is optionally partially or fully halogenated, phenyloxy, naphthyloxy, nitro, amino, mono- or di- (C_{1-3}) alkylamino, phenylamino, naphthylamino, aminocarbonyl, mono- or di-(C_{1-3}) alkylaminocarbonyl, amino(C_{1-5})alkyl or alkenyl, di-(C_{1-3})alkylamino(C_{1-5})alkyl or alkenyl, phenylamino(C_{1-3})alkyl or alkenyl, naphthylamino(C_{1-3})alkyl or alkenyl, phenylamido(C_{1-3})alkyl or alkenyl, naphthylamido(C_{1-3})alkyl or alkenyl, phenyl(C_{1-5})alkyl or alkenyl and naphthyl(C_{1-5})alkyl or alkenyl;

b) fused aryl (selected from benzocyclobutanyl, indanyl, indenyl, dihydronaphthyl, tetrahydronaphthyl, benzocycloheptanyl and benzocycloheptenyl), and fused heteroaryl (selected from cyclopentenopyridine, cyclohexanopyridine, cyclopentanopyrimidine, cyclohexanopyrimidine, cyclopentanopyrazine, cyclohexanopyrazine, cyclopentanopyridazine, cyclohexanopyridazine, cyclopentanoquinoline, cyclohexanoquinoline, cyclopentanoisoquinoline, cyclohexanoisoquinoline, cyclopentanoindole, cyclohexanoindole, cyclopentanobenzimidazole, cyclohexanobenzimidazole, cyclopentanobenzoxazole, cyclohexanobenzoxazole, cyclopentanoimidazole, cyclohexanoimidazole, cyclopentanothiophene and cyclohexanothiophene), wherein the fused aryl or fused heteroaryl ring bears 0 to 3 groups selected from phenyl, naphthyl, heteroaryl (wherein such heteroaryl is selected from pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrrolyl, imidazolyl, pyrazolyl, thienyl, furyl, isoxazolyl and isothiazolyl), C_{1-6} branched or unbranched alkyl which is optionally partially or fully halogenated, halo, cyano, C_{1-3} alkyloxy which is optionally partially or fully halogenated, phenyloxy, naphthyloxy, nitro, amino, mono- or di- (C_{1-3}) alkylamino, phenylamino, naphthylamino, aminocarbonyl, mono- or di-(C_{1-3}) alkylaminocarbonyl, amino(C_{1-5})alkyl or alkenyl, di-(C_{1-3})alkylamino(C_{1-5})alkyl or alkenyl, phenylamino(C_{1-3})alkyl or alkenyl, naphthylamino(C_{1-3})alkyl or alkenyl, phenylamido(C_{1-3})alkyl or alkenyl, naphthylamido(C_{1-3})alkyl or alkenyl, phenyl(C_{1-5})alkyl or alkenyl and naphthyl(C_{1-5})alkyl or alkenyl;

c) cycloalkyl selected from cyclopentanyl, cyclohexanyl, cycloheptanyl, bicyclopentanyl, bicyclohexanyl and bicycloheptanyl, which cycloalkyl group is optionally partially or fully halogenated and which is optionally substituted with one to three C_{1-3} alkyl groups;

d) cycloalkenyl selected from cyclopentenyl, cyclohexenyl, cyclohexadienyl, cycloheptenyl, cycloheptadienyl, bicyclohexenyl and bicycloheptenyl, which cycloalkenyl group is optionally partially or fully

halogenated and which is optionally substituted with one to three C_{1-3} alkyl groups; and

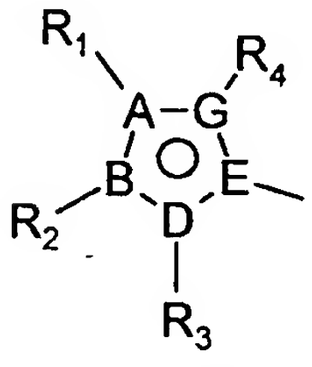
e) phenyl(C_{1-5} branched or unbranched)alkyl, and naphthyl(C_{1-5} branched or unbranched)alkyl, wherein the phenyl or naphthyl ring is substituted with 0 to 5 groups selected from the group consisting of phenyl, naphthyl, heteroaryl (selected from pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrrolyl, imidazolyl, pyrazolyl, thienyl, furyl, isoxazolyl and isothiazolyl), C_{1-6} branched or unbranched alkyl which is optionally partially or fully halogenated, halo, cyano, C_{1-3} alkyloxy which is optionally partially or fully halogenated, phenyloxy, naphthyloxy or heteroaryloxy (wherein the heteroaryl moiety is as defined above in this subparagraph);

R_6 is hydrogen, cyano or C_{1-6} branched or unbranched alkyl which is optionally partially or fully halogenated; and,

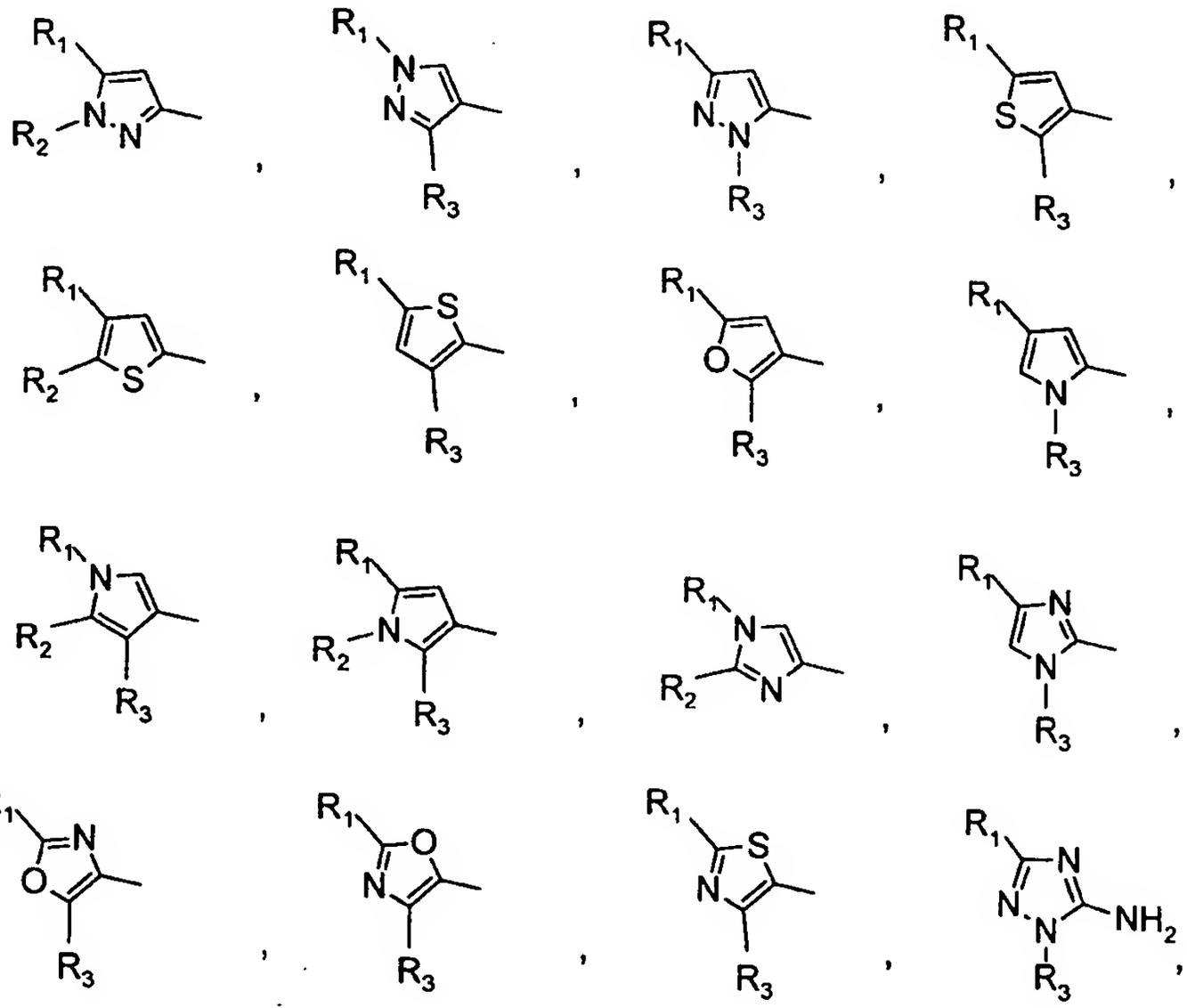
R_7 is hydrogen or C_{1-6} branched or unbranched alkyl, which is optionally partially or fully halogenated.

In a somewhat preferred generic aspect, the invention comprises compounds of the above formula I, wherein:

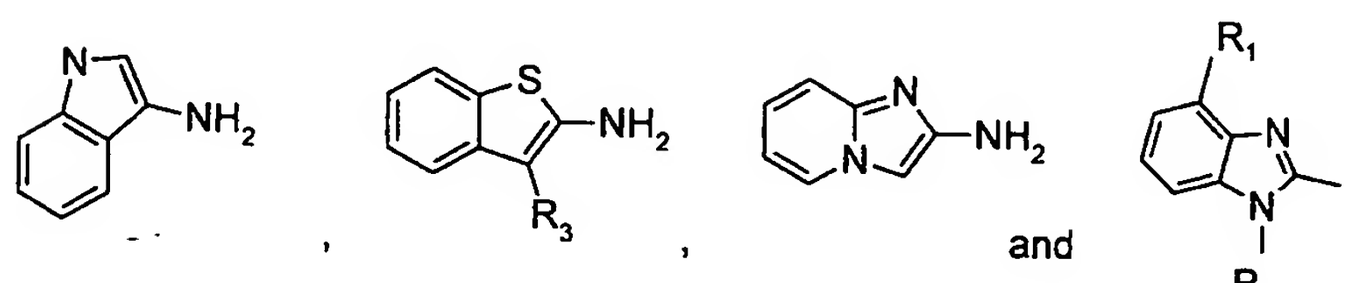
the heterocyclic moiety



is selected from the group consisting of:



and



;

X is S, O or NR_6;

Y is N-H;

R_1 is selected from the group consisting of:

a) C_{3-10} branched alkyl, which is optionally partially or fully halogenated, and optionally substituted with one to three phenyl, naphthyl or heteroaryl groups (each such heteroaryl group being independently selected from pyridinyl and thienyl), each such phenyl, naphthyl or heteroaryl group being substituted with 0 to 5 groups selected from halogen, C_{1-6} branched or unbranched alkyl which is optionally partially or fully halogenated, C_{3-8} cycloalkyl, C_{5-8} cycloalkenyl, hydroxy, cyano, C_{1-3} alkyloxy which is optionally partially or fully halogenated, aminocarbonyl and di(C_{1-3})alkylaminocarbonyl;

b) a cycloalkyl group selected from cyclopropyl, cyclobutyl, cyclopentanyl, cyclohexanyl, cycloheptanyl, bicyclopentanyl, bicyclohexanyl and bicycloheptanyl, which cycloalkyl group is optionally partially or fully halogenated and which is optionally substituted with one to three C_{1-3} alkyl groups, or an analog of such cycloalkyl group wherein instead of one to three ring methylene groups there are groups independently selected from O, S, CHOH, >C=O, >C=S and NH;

c) C_{3-10} branched alkenyl which is optionally partially or fully halogenated, and which is optionally substituted with one to three groups independently selected from C_{1-5} branched or unbranched alkyl, phenyl, naphthyl or heteroaryl, with each such heteroaryl group being independently selected from pyridinyl and thienyl and each such phenyl, naphthyl or heteroaryl group being substituted with 0 to 5 groups selected from halogen, C_{1-6} branched or unbranched alkyl which is optionally partially or fully halogenated, cyclopropyl, cyclobutyl, cyclopentanyl, cyclohexanyl, cycloheptanyl, bicyclopentanyl, bicyclohexanyl, bicycloheptanyl, hydroxy, cyano, C_{1-3} alkyloxy which is optionally partially or fully halogenated, aminocarbonyl and mono- or di(C_{1-3})alkylaminocarbonyl;

d) a cycloalkenyl group selected from cyclopentenyl, cyclohexenyl, cyclohexadienyl, cycloheptenyl, cycloheptadienyl, bicyclohexenyl and

bicycloheptenyl, wherein such cycloalkenyl group is optionally substituted with one to three C_{1-3} alkyl groups;

e) an alkoxy carbonyl group selected from methoxycarbonyl, ethoxycarbonyl and propoxycarbonyl;

R_2 is selected from the group consisting of the following, when B is a carbon atom or an amino nitrogen: hydrogen, C_{1-6} branched or unbranched alkyl which is optionally partially or fully halogenated, benzoyl and phenylsulfonyl;

R_3 is selected from the group consisting of the following, when D is a carbon atom or an amino nitrogen:

a) phenyl, naphthyl and heteroaryl (wherein said heteroaryl group is selected from pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrrolyl, imidazolyl, pyrazolyl, thienyl, furyl, isoxazolyl, isothiazolyl, quinolinyl, isoquinolinyl, indolyl, benzimidazolyl, benzofuranyl and benzoxazolyl), wherein such phenyl, naphthyl or heteroaryl group is optionally substituted with one to three groups independently selected from C_{1-6} branched or unbranched alkyl, phenyl, naphthyl, heteroaryl selected from the group set forth immediately above, C_{1-6} branched or unbranched alkyl which is optionally partially or fully halogenated, cyclopropyl, cyclobutyl, cyclopentanyl, cyclohexanyl, cycloheptanyl, bicyclopentanyl, bicyclohexanyl, bicycloheptanyl, phenyl C_{1-5} alkyl, naphthyl C_{1-5} alkyl, halo, hydroxy, cyano, C_{1-3} alkyloxy which is optionally partially or fully halogenated, phenyloxy, naphthyloxy, heteraryloxy wherein the heteroaryl moiety is selected from the group set forth above in this subparagraph, nitro, amino, mono- or di-(C_{1-3})alkylamino, phenylamino, naphthylamino, heteroarylamino wherein the heteroaryl moiety is selected from the group set forth above in this subparagraph, aminocarbonyl, a mono- or di-(C_{1-3})alkyl aminocarbonyl, C_{1-4} branched or unbranched alkyl oxycarbonyl, C_{1-5} alkylcarbonyl C_{1-4} branched or unbranched alkyl, amino C_{1-5} alkyl, mono- or di-(C_{1-3})alkylamino(C_{1-5})alkyl, aminosulfonyl, di-(C_{1-3})alkylaminosulfonyl;

b) fused aryl (selected from benzocyclobutanyl, indanyl, indenyl, dihydronaphthyl, tetrahydronaphthyl, benzocycloheptanyl and benzocycloheptenyl), and fused heteroaryl (selected from cyclopentenopyridine, cyclohexanopyridine, cyclopentanothiophene and cyclohexanothiophene), wherein the fused aryl or fused heteroaryl ring is substituted with 0 to 3 groups independently selected from phenyl, naphthyl and heteroaryl (wherein each such heteroaryl is selected from pyridinyl and thienyl), C_{1-6} branched or unbranched alkyl which is optionally partially or fully halogenated, halo, cyano, C_{1-3} alkyloxy which is optionally partially or fully halogenated, phenyloxy, naphthyloxy, heteroaryloxy (wherein the heteroaryl moiety is selected from the group set forth above in this subparagraph), amino, mono- or di-(C_{1-3})alkylamino, phenylamino, naphthylamino, heteroarylamino (wherein the heteroaryl moiety is selected from the group set forth above in this subparagraph), aminocarbonyl, a mono- or di-(C_{1-3})alkyl aminocarbonyl, C_{1-4} branched or unbranched alkyl oxycarbonyl, C_{1-5} alkylcarbonyl C_{1-4} branched or unbranched alkyl, amino C_{1-5} alkyl, mono- or di-(C_{1-3})alkylamino(C_{1-5})alkyl, aminosulfonyl, di-(C_{1-3})alkylaminosulfonyl;

c) a cycloalkyl group selected from cyclopentanyl, cyclohexanyl and cycloheptanyl, which cycloalkyl group is optionally partially or fully halogenated and which is optionally substituted with one to three C_{1-3} alkyl groups;

d) a cycloalkenyl group selected from cyclopentenyl, cyclohexenyl and cycloheptenyl, wherein such cycloalkenyl group is optionally substituted with one to three C_{1-3} alkyl groups; and,

e) acetyl, benzoyl and phenylsulfonyl;

or R_1 and R_2 taken together may optionally form a fused phenyl or pyridinyl ring,

or R_2 and R_3 taken together may optionally form a fused phenyl or pyridinyl ring,

R_5 is selected from the group consisting of:

a) phenyl, naphthyl and heteroaryl (wherein such heteroaryl is selected from pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrazolyl, thienyl, quinolinyl, isoquinolinyl, indolyl, benzimidazolyl, benzofuranyl, benzoxazolyl, benzisoxazolyl), wherein such phenyl, naphthyl or heteroaryl group optionally bears one to three groups selected from phenyl, naphthyl and heteroaryl (wherein each such heteroaryl moiety is independently selected from the group defined above in this subparagraph), C_{1-6} branched or unbranched alkyl which is optionally partially or fully halogenated, cyclopropyl, cyclobutyl, cyclopentanyl, cyclohexanyl, halo, cyano, C_{1-3} alkyloxy which is optionally partially or fully halogenated, phenyloxy, naphthyloxy, mono- or di- (C_{1-3}) alkylamino, phenylamino, naphthylamino, mono- or di-(C_{1-3}) alkylaminocarbonyl, amino(C_{1-5})alkyl or alkenyl, di-(C_{1-3})alkylamino(C_{1-5})alkyl or alkenyl, phenylamino(C_{1-3})alkyl or alkenyl, naphthylamino(C_{1-3})alkyl or alkenyl, phenylamido(C_{1-3})alkyl or alkenyl, naphthylamido(C_{1-3})alkyl or alkenyl, phenyl(C_{1-5})alkyl or alkenyl and naphthyl(C_{1-5})alkyl or alkenyl;

b) fused aryl (selected from benzocyclobutanyl, indanyl, indenyl, dihydronaphthyl, tetrahydronaphthyl, benzocycloheptanyl and benzocycloheptenyl), and fused heteroaryl (selected from cyclopentenopyridine, cyclohexanopyridine, cyclopentanothiophene and cyclohexanothiophene), wherein the fused aryl or fused heteroaryl ring bears 0 to 3 groups selected from phenyl, naphthyl, heteroaryl (wherein such heteroaryl is selected from pyridinyl and thienyl), C_{1-6} branched or unbranched alkyl which is optionally partially or fully halogenated, halo, cyano, C_{1-3} alkyloxy which is optionally partially or fully halogenated, phenyloxy, naphthyloxy, amino, mono- or di- (C_{1-3}) alkylamino, phenylamino, naphthylamino, aminocarbonyl, mono- or di-(C_{1-3}) alkylaminocarbonyl, amino(C_{1-5})alkyl or alkenyl, di-(C_{1-3})alkylamino(C_{1-5})alkyl or alkenyl, phenylamino(C_{1-3})alkyl or alkenyl, naphthylamino(C_{1-3})alkyl or alkenyl, phenylamido(C_{1-3})alkyl or alkenyl, naphthylamido(C_{1-3})alkyl or alkenyl, phenyl(C_{1-5})alkyl or alkenyl and naphthyl(C_{1-5})alkyl or alkenyl;

$_3$)alkyl or alkenyl, phenyl(C_{1-5})alkyl or alkenyl and naphthyl(C_{1-5})alkyl or alkenyl;

c) cycloalkyl selected from cyclopentanyl, cyclohexanyl and cycloheptanyl, which cycloalkyl group is optionally partially or fully halogenated and which is optionally substituted with one to three C_{1-3} alkyl groups;

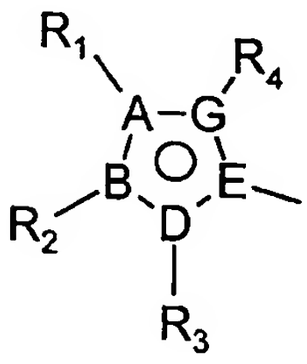
d) cycloalkenyl selected from cyclopentenyl and cyclohexenyl, which cycloalkenyl group is optionally partially or fully halogenated and which is optionally substituted with one to three C_{1-3} alkyl groups; and

e) phenyl(C_{1-5} branched or unbranched)alkyl, and naphthyl(C_{1-5} branched or unbranched)alkyl, wherein the phenyl or naphthyl ring is substituted with 0 to 5 groups selected from the group consisting of phenyl, naphthyl, heteroaryl (selected from pyridinyl and thienyl), C_{1-6} branched or unbranched alkyl which is optionally partially or fully halogenated, halo, cyano, C_{1-3} alkyloxy which is optionally partially or fully halogenated, phenyloxy, naphthyloxy or heteroaryloxy (wherein the heteroaryl moiety is as defined above in this subparagraph);

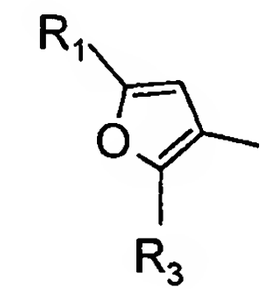
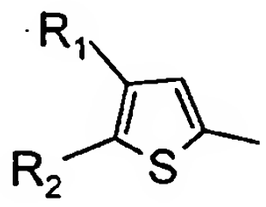
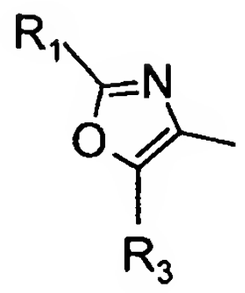
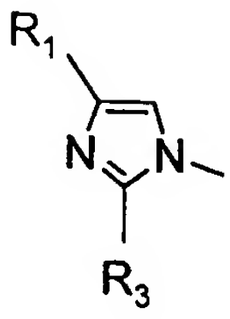
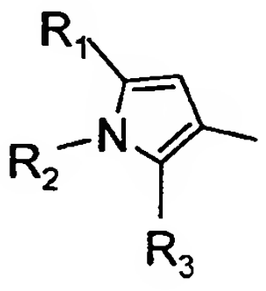
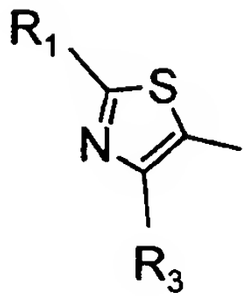
R_6 is hydrogen, cyano or C_{1-6} branched or unbranched alkyl which is optionally partially or fully halogenated.

In a penultimately preferred generic aspect, the invention provides compounds of the above formula I, wherein:

the heterocyclic moiety



is selected from the group consisting of:


,

,

,

,

and

;

X is S or O;

Y is N-H;

R_1 is selected from the group consisting of:

a) C_{3-10} branched alkyl, which is optionally partially or fully halogenated, and optionally substituted with one to three phenyl, naphthyl or heteroaryl groups (each such heteroaryl group being independently selected from pyridinyl and thienyl), each such phenyl, naphthyl or heteroaryl group being substituted with 0 to 3 groups selected from halogen, C_{1-6} branched or unbranched alkyl which is optionally partially

or fully halogenated, C_{3-8} cycloalkyl, hydroxy, cyano and C_{1-3} alkyloxy which is optionally partially or fully halogenated;

b) a cycloalkyl group selected from cyclopropyl, cyclobutyl, cyclopentanyl, cyclohexanyl, cycloheptanyl, bicyclopentanyl, bicyclohexanyl and bicycloheptanyl, which cycloalkyl group is optionally partially or fully halogenated and which is optionally substituted with one to three C_{1-3} alkyl groups, or an analog of such cycloalkyl group wherein instead of one to three ring methylene groups there are groups independently selected from O, S, CHOH, >C=O, >C=S and NH;

c) C_{3-10} branched alkenyl which is optionally partially or fully halogenated, and which is optionally substituted with one to three groups independently selected from C_{1-5} branched or unbranched alkyl, phenyl, naphthyl or heteroaryl, with each such heteroaryl group being independently selected from pyridinyl and thienyl and each such phenyl, naphthyl or heteroaryl group being substituted with 0 to 3 groups selected from halogen, C_{1-6} branched or unbranched alkyl which is optionally partially or fully halogenated, cyclopropyl, cyclobutyl, cyclopentanyl, hydroxy, cyano, and C_{1-3} alkyloxy which is optionally partially or fully halogenated;

d) a cycloalkenyl group selected from cyclopentenyl, cyclohexenyl, bicyclohexenyl and bicycloheptenyl, wherein such cycloalkenyl group is optionally substituted with one to three C_{1-3} alkyl groups;

e) an alkoxy carbonyl group selected from methoxycarbonyl, ethoxycarbonyl and propoxycarbonyl;

R_2 is selected from the group consisting of the following, when B is a carbon atom or an amino nitrogen: hydrogen, C_{1-6} branched or unbranched alkyl which is optionally partially or fully halogenated, acetyl, benzoyl and phenylsulfonyl;

R_3 is selected from the group consisting of the following, when D is a carbon atom or an amino nitrogen:

a) phenyl, naphthyl and heteroaryl (wherein said heteroaryl group is selected from pyridinyl, quinolinyl and isoquinolinyl), wherein such phenyl, naphthyl or heteroaryl group is optionally substituted with one to three groups independently selected from C_{1-6} branched or unbranched alkyl, phenyl, naphthyl, heteroaryl selected from the group set forth immediately above, C_{1-6} branched or unbranched alkyl which is optionally partially or fully halogenated, cyclopropyl, cyclobutyl, cyclopentanyl, cyclohexanyl, phenyl C_{1-5} alkyl, halo, hydroxy, cyano, C_{1-3} alkyloxy which is optionally partially or fully halogenated, phenyloxy, naphthyloxy, heteraryloxy wherein the heteroaryl moiety is selected from the group set forth above in this subparagraph, mono- or di-(C_{1-3})alkylamino, phenylamino, naphthylamino, heteroarylamino wherein the heteroaryl moiety is selected from the group set forth above in this subparagraph, aminocarbonyl, a mono- or di-(C_{1-3})alkyl aminocarbonyl, C_{1-5} alkylcarbonyl C_{1-4} branched or unbranched alkyl, amino C_{1-5} alkyl and mono- or di-(C_{1-3})alkylamino(C_{1-5})alkyl;

b) fused aryl (selected from benzocyclobutanyl, indanyl, indenyl, dihydronaphthyl and tetrahydronaphthyl), and fused heteroaryl (selected from cyclopentenopyridine, cyclohexanopyridine, cyclopentanothiophene and cyclohexanothiophene), wherein the fused aryl or fused heteroaryl ring is substituted with 0 to 3 groups independently selected from phenyl, naphthyl and heteroaryl (wherein each such heteroaryl is selected from pyridinyl and thienyl), C_{1-6} branched or unbranched alkyl which is optionally partially or fully halogenated, halo, cyano, C_{1-3} alkyloxy which is optionally partially or fully halogenated, phenyloxy, naphthyloxy, heteroaryloxy (wherein the heteroaryl moiety is selected from the group set forth above in this subparagraph), mono- or di-(C_{1-3})alkylamino, phenylamino, naphthylamino, heteroarylamino (wherein the heteroaryl moiety is selected from the group set forth above in this subparagraph), aminocarbonyl, a mono- or di-(C_{1-3})alkyl aminocarbonyl, amino C_{1-5} alkyl and mono- or di-(C_{1-3})alkylamino(C_{1-5})alkyl;

c) a cycloalkyl group selected from cyclopentanyl, cyclohexanyl and cycloheptanyl, which cycloalkyl group is optionally partially or fully halogenated and which is optionally substituted with one to three C_{1-3} alkyl groups;

d) a cycloalkenyl group selected from cyclopentenyl, cyclohexenyl and cycloheptenyl, wherein such cycloalkenyl group is optionally substituted with one to three C_{1-3} alkyl groups;

e) acetyl, benzoyl and phenylsulfonyl; and,

or R_1 and R_2 taken together may optionally form a fused phenyl or pyridinyl ring,

R_5 is selected from the group consisting of:

a) phenyl, naphthyl and heteroaryl (wherein such heteroaryl is selected from pyridinyl, thienyl, quinolinyl, isoquinolinyl and indolyl), wherein such phenyl, naphthyl or heteroaryl group optionally bears one to three groups selected from phenyl, naphthyl and heteroaryl (wherein each such heteroaryl moiety is independently selected from the group defined above in this subparagraph), C_{1-6} branched or unbranched alkyl which is optionally partially or fully halogenated, cyclopropyl, cyclobutyl, cyclopentanyl, cyclohexanyl, halo, cyano, C_{1-3} alkyloxy which is optionally partially or fully halogenated, phenyloxy, naphthyloxy, , phenylamino, naphthylamino phenylamino(C_{1-3})alkyl or alkenyl, naphthylamino(C_{1-3})alkyl or alkenyl, phenylamido(C_{1-3})alkyl or alkenyl, naphthylamido(C_{1-3})alkyl or alkenyl, heteroarylamido(C_{1-3})alkyl or alkenyl (wherein the heteroaryl moiety is as defined above in this subparagraph);

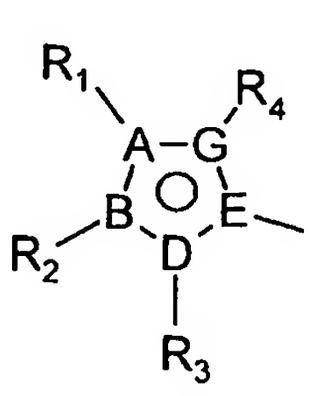
b) fused aryl (selected from benzocyclobutanyl, indanyl, indenyl, dihydronaphthyl, tetrahydronaphthyl, benzocycloheptanyl and benzocycloheptenyl), and fused heteroaryl (selected from cyclopentenopyridine, cyclohexanopyridine, cyclopentanothiophene and cyclohexanothiophene), wherein the fused aryl or fused heteroaryl ring bears 0 to 3 groups selected from phenyl, naphthyl, heteroaryl (wherein

such heteroaryl is selected from pyridinyl and thienyl), C_{1-6} branched or unbranched alkyl which is optionally partially or fully halogenated, halo, cyano, C_{1-3} alkyloxy which is optionally partially or fully halogenated, phenyloxy, naphthyloxy, , phenylamino, naphthylamino, phenylamino(C_{1-3})alkyl or alkenyl, naphthylamino(C_{1-3})alkyl or alkenyl, phenylamido(C_{1-3})alkyl or alkenyl, naphthylamido(C_{1-3})alkyl or alkenyl, heteroarylamido(C_{1-3})alkyl or alkenyl (wherein the heteroaryl moiety is as defined above in this subparagraph); and,

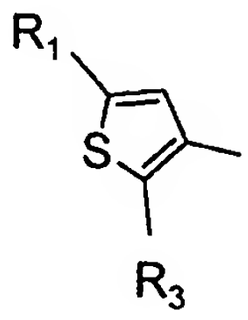
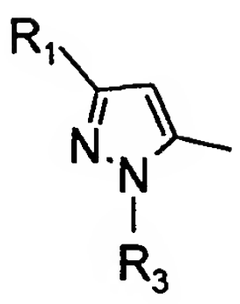
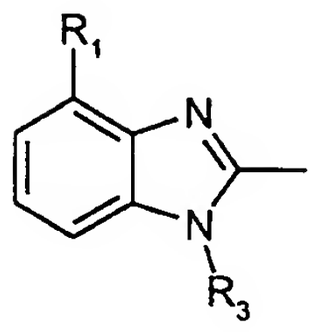
c) phenyl(C_{1-5} branched or unbranched)alkyl, and naphthyl(C_{1-5} branched or unbranched)alkyl, wherein the phenyl or naphthyl ring is substituted with 0 to 3 groups selected from the group consisting of phenyl, naphthyl, heteroaryl (selected from pyridinyl and thienyl), C_{1-6} branched or unbranched alkyl which is optionally partially or fully halogenated, halo, cyano, C_{1-3} alkyloxy which is optionally partially or fully halogenated, phenyloxy, naphthyloxy or heteroaryloxy (wherein the heteroaryl moiety is as defined above in this subparagraph).

In an ultimately preferred generic aspect, the invention provides compounds of the formula I, wherein:

the heterocyclic moiety



is selected from the group consisting of:

;

X is S or O;

Y is N-H;

R_1 is selected from the group consisting of:

a) C_{3-7} branched alkyl, which is optionally partially or fully halogenated, and optionally substituted with one to three phenyl or heteroaryl groups (each such heteroaryl group being independently selected from pyridinyl and thienyl), each such phenyl or heteroaryl group being substituted with 0 to 3 groups selected from halogen, C_{1-6} branched or unbranched alkyl which is optionally partially or fully halogenated, C_{3-8} cycloalkyl and C_{1-3} alkyloxy which is optionally partially or fully halogenated;

b) a cycloalkyl group selected from cyclopropyl, cyclobutyl, cyclopentanyl, cyclohexanyl, cycloheptanyl, bicyclopentanyl, bicyclohexanyl and bicycloheptanyl, which cycloalkyl group is optionally partially or fully halogenated and which is optionally substituted with one to three C_{1-3} alkyl groups;

c) C_{3-7} branched alkenyl which is optionally partially or fully halogenated, and which is optionally substituted with one to three groups independently selected from C_{1-5} branched or unbranched alkyl, phenyl or heteroaryl, with each such heteroaryl group being independently selected from pyridinyl and thienyl and each such phenyl or heteroaryl group being substituted with 0 to 3 groups selected from halogen, C_{1-6} branched or unbranched alkyl which is optionally partially or fully halogenated, cyclopropyl, cyclobutyl, cyclopentanyl and C_{1-3} alkyloxy which is optionally partially or fully halogenated;

R_2 is selected from the group consisting of the following, when B is a carbon atom or an amino nitrogen: hydrogen, C_{1-6} branched or unbranched alkyl which is optionally partially or fully halogenated, acetyl, benzoyl and phenylsulfonyl;

R_3 is selected from the group consisting of the following, when D is a carbon atom or an amino nitrogen:

a) phenyl, naphthyl and heteroaryl (wherein said heteroaryl group is selected from pyridinyl, quinolinyl and isoquinolinyl), wherein such phenyl, naphthyl or heteroaryl group is optionally substituted with one to three groups independently selected from C_{1-6} branched or unbranched alkyl, phenyl, naphthyl, heteroaryl selected from the group set forth immediately above, C_{1-6} branched or unbranched alkyl which is optionally partially or fully halogenated, cyclopropyl, cyclobutyl, cyclopentanyl, cyclohexanyl, halo, hydroxy, cyano, C_{1-3} alkyloxy which is optionally partially or fully halogenated, phenyloxy, heteraryloxy wherein the heteroaryl moiety is selected from the group set forth above in this subparagraph, mono- or di-(C_{1-3})alkylamino, phenylamino, heteroarylamino wherein the heteroaryl moiety is selected from the group set forth above in this subparagraph, aminocarbonyl, a mono- or di-(C_{1-3})alkyl aminocarbonyl and mono- or di-(C_{1-3})alkylamino(C_{1-5})alkyl;

b) fused aryl (selected from benzocyclobutanyl, indanyl, indenyl, dihydronaphthyl and tetrahydronaphthyl), and fused heteroaryl (selected from cyclopentenopyridine, cyclohexanopyridine, cyclopentanothiophene and cyclohexanothiophene), wherein the fused aryl or fused heteroaryl ring is substituted with 0 to 3 groups independently selected from phenyl and heteroaryl (wherein each such heteroaryl is selected from pyridinyl and thienyl), C_{1-6} branched or unbranched alkyl which is optionally partially or fully halogenated, halo, cyano, C_{1-3} alkyloxy which is optionally partially or fully halogenated, phenyloxy, heteroaryloxy (wherein the heteroaryl moiety is selected from the group set forth above in this subparagraph), mono- or di-(C_{1-}

$_3$)alkylamino, phenylamino, heteroarylamino (wherein the heteroaryl moiety is selected from the group set forth above in this subparagraph), aminocarbonyl, a mono- or di-(C_{1-3})alkyl aminocarbonyl and mono- or di-(C_{1-3})alkylamino(C_{1-5})alkyl;

c) a cycloalkyl group selected from cyclopentanyl, cyclohexanyl and cycloheptanyl, which cycloalkyl group is optionally partially or fully halogenated and which is optionally substituted with one to three C_{1-3} alkyl groups;

d) acetyl, benzoyl and phenylsulfonyl; and,

or R_1 and R_2 taken together may optionally form a fused phenyl or pyridinyl ring,

R_5 is selected from the group consisting of:

a) phenyl, naphthyl and heteroaryl (wherein such heteroaryl is selected from pyridinyl, thienyl, quinolinyl and isoquinolinyl), wherein such phenyl, naphthyl or heteroaryl group optionally bears one to three groups selected from phenyl and heteroaryl (wherein each such heteroaryl moiety is independently selected from the group defined above in this subparagraph), C_{1-6} branched or unbranched alkyl which is optionally partially or fully halogenated, cyclopropyl, cyclobutyl, cyclopentanyl, cyclohexanyl, halo, cyano, C_{1-3} alkyloxy which is optionally partially or fully halogenated, phenyloxy, phenylamino;

b) fused aryl (selected from benzocyclobutanyl, indanyl, indenyl, dihydronaphthyl, tetrahydronaphthyl, benzocycloheptanyl and benzocycloheptenyl), and fused heteroaryl (selected from cyclopentenopyridine, cyclohexanopyridine, cyclopentanothiophene and cyclohexanothiophene), wherein the fused aryl or fused heteroaryl ring bears 0 to 3 groups selected from phenyl, C_{1-6} branched or unbranched alkyl which is optionally partially or fully halogenated, halo, cyano, C_{1-3} alkyloxy which is optionally partially or fully halogenated, phenyloxy and phenylamino; and,

c) phenyl(C_{1-5} branched or unbranched)alkyl, and naphthyl(C_{1-5} branched or unbranched)alkyl, wherein the phenyl or naphthyl ring is substituted with 0 to 3 groups selected from the group consisting of phenyl, C_{1-6} branched or unbranched alkyl which is optionally partially or fully halogenated, halo, cyano, C_{1-3} alkyloxy which is optionally partially or fully halogenated and phenyloxy.

Specifically preferred compounds in accordance with the invention are those selected from the group consisting of:

1-[5-*tert*-Butyl-2-(2-methylpyridin-5-yl)-2H-pyrazol-3-yl]-3-(4-chlorophenyl)urea;

1-(5-*tert*-Butyl-2-*p*-tolyl-2H-pyrazol-3-yl)-3-(4-methoxynaphthalen-1-yl)urea;

1-(5-*tert*-Butyl-2-(3,4-dimethylphenyl)-2H-pyrazol-3-yl)-3-(4-fluorophenyl)urea;

1-(5-*tert*-Butyl-2-*p*-tolyl-2H-pyrazol-3-yl)-3-(2-fluorophenyl)urea; and

1-[5-*tert*-Butyl-2-(pyridin-3-yl)-2H-pyrazol-3-yl]-3-(4-cyanonaphthalen-1-yl)urea.

Any compounds of this invention containing one or more asymmetric carbon atoms may occur as racemates and racemic mixtures, single enantiomers, diastereomeric mixtures and individual diastereomers. All such isomeric forms of these compounds are expressly included in the present invention. Each stereogenic carbon may be in the R or S configuration, or a combination of configurations.

Some of the compounds of formula I can exist in more than one tautomeric form. The invention includes all such tautomers.

The invention includes pharmaceutically acceptable derivatives of compounds of formula I. A "pharmaceutically acceptable derivative" refers to any pharmaceutically acceptable salt or ester of a compound of this invention, or any other compound which, upon administration to a patient, is capable of providing (directly or indirectly) a

compound of this invention, a pharmacologically active metabolite or pharmacologically active residue thereof.

Pharmaceutically acceptable salts of the compounds of the invention include those derived from pharmaceutically acceptable inorganic and organic acids and bases. Examples of suitable acids include hydrochloric, hydrobromic, sulfuric, nitric, perchloric, fumaric, maleic, phosphoric, glycolic, lactic, salicylic, succinic, toluene-p-sulfuric, tartaric, acetic, citric, methanesulfonic, formic, benzoic, malonic, naphthalene-2-sulfuric and benzenesulfonic acids. Other acids, such as oxalic acid, while not themselves pharmaceutically acceptable, may be employed in the preparation of salts useful as intermediates in obtaining the compounds of this invention and their pharmaceutically acceptable acid addition salts. Salts derived from appropriate bases include alkali metal (*e.g.*, sodium), alkaline earth metal (*e.g.*, magnesium), ammonium and N-(C_1-C_4 alkyl)$_4^+$ salts.

In addition, the invention include prodrugs of the compounds of compounds of the formula I. Prodrugs include those compounds that, upon simple chemical transformation, are modified to produce a compound of formula I. Simple chemical transformations include hydrolysis, oxidation and reduction. Specifically, when a prodrug of this invention is administered to a patient, the prodrug may be transformed into a compound of formula I, thereby imparting the desired pharmacological effect.

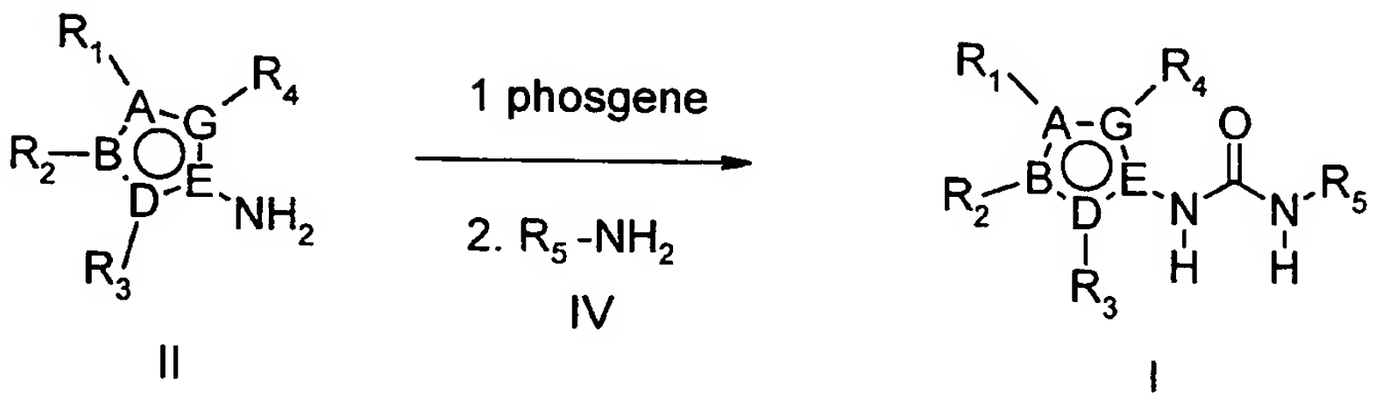
GENERAL SYNTHETIC METHODS

The compounds of the invention may be prepared by Method A or B as illustrated in Scheme I.

Scheme I

Method A

Method B



In Method A, a mixture of an aminoheterocycle of formula II and an arylisocyanate of formula III is dissolved in a non-protic, anhydrous solvent such as THF, ether, toluene, dioxane or ethyl acetate. The preferred solvent is THF. The mixture is stirred at between 0 - 45° C, preferably at 25° C, for 2-24 hr, and the volatiles are removed. Purification of the residue by recrystallization or silica gel chromatography, using hexanes and ethyl acetate as eluents, provides the product of formula I.

In Method B, an aminoheterocycle of formula II is dissolved in a halogenated solvent, such as methylene chloride, chloroform or dichloroethane. The preferred solvent is methylene chloride. The mixture is diluted with aqueous alkali, such as sodium bicarbonate or potassium carbonate, cooled in an ice bath and phosgene is added. The

mixture is vigorously stirred for 5 – 30 min, with 10 min being preferable. The organic layer is dried, with agents such as $MgSO_4$ or Na_2SO_4, and the volatiles removed to provide the corresponding isocyanate of formula II. The isocyanate and arylamine IV are mixed in a non-protic, anhydrous solvent such as THF, ether, toluene, dioxane, methylene chloride or ethyl acetate. The preferred solvent is THF. The mixture is stirred at between 0 - 45° C, preferably at 25° C, for 2 - 24 hr, and the volatiles are removed. Purification of the residue by recrystallization or silica gel chromatography, using hexanes and ethyl acetate as eluents, provides the product of formula I.

The method used to produce an aminoheterocycle of formula II will depend on the nature of the desired heterocycle. In general, intermediates of formula II can be made by methods known to those skilled in the art. Some general methods are illustrated in the schemes below. Amines and isocyanates bearing R_5 used in Method A or B respectively are available commercially or easily prepared by methods known to those skilled in the art.

Desired aminopyrazoles of formula XII can be prepared as described in Scheme II. A hydrazine of formula VII, bearing substituent R_3, may be prepared by Method C or D. In Method C, an aryl bromide of formula V is dissolved in a non-protic, inert solvent, such as THF, 1,4-dioxane or diethyl ether, and cooled to low temperature under an inert atmosphere. The preferred temperature for the solution is –77° C. A strong base dissolved in a non-protic, inert solvent, such as hexanes, THF or ether, is added dropwise while maintaing a reaction temperature below 0° C and preferrably below –60° C. The preferred bases are alkyl lithium reagents and the most preferred is *sec*-butyl lithium. After the addition of the base, the reaction mixture is stirred for a period of time between thirty and ninety minutes or until all the starting aryl bromide has been consumed. An excess of dialkyl azodicarboxylate is added while maintaining a reaction temperature below 0° C and preferrably below –60° C. The preferred dialkyl azodicarboxylate is di-*tert*-butyl azodicarboxylate. The reaction is stirred at cold temperatures and warmed to room temperature after 0.5 hr to 2 hr. The reaction is quenched with the addition of water and the product extracted into a non-protic solvent, such as ethyl acetate, diethyl ether or chloroform. The organic layers are dried with

agents such as $MgSO_4$ or Na_2SO_4 and the volatiles removed. The residue is dissolved in protic solvents, such as methanol or *iso*-propanol, cooled, preferably to 0-5° C and treated with acid. Preferred acids are hydrochloric, hydrobromic, sulfuric and trifluoroacetic. The most preferred is hydrochloric in gaseous form. After the addition of excess acid the mixture is heated at the reflux temperature of the solvent until all starting material has been consumed. After cooling the product aryl-hydrazine of formula VII salt is filtered and dried.

Scheme II